Research Article

A real life experience with novel biosimilar Infimab™ in biologic naive patients with active rheumatoid arthritis

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Abstract

Objective: To determine the efficacy and safety of novel infliximab biosimilar, Infimab™ (IFB) in rheumatoid arthritis (RA) patients. **Materials and Methods:** Eight patients with active RA who failed to demonstrate clinical improvement with methotrexate were enrolled. Post consent, patients were administered infliximab biosimilar 3mg/kg body weight as intra venous infusion at weeks 0, 2, 6 then every 8 weeks on demand. Patients were assessed for Health assessment questionnaire (HAQ, India Score), disease activity score 28 (DAS 28), Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC), erythrocyte sedimentation rate (ESR) and Visual Analogue Scale (VAS) score at baseline and at each visit. They were also observed for any adverse effects or tuberculosis infection. Wilcoxon sign rank test was used to assess the change between baseline to each follow-up visit. **Results:** On any average 3 infusions were administered to patients. At visit 3 there was significant improvement in HAQ score (p=0.046), WOMAC score (p=0.018), Tender joints count (p=0.027), swollen joints count (p=0.027) and also in general health (p=0.043). Though the VAS scores and ESR values decreased at visit 3, they were not significant. At the end of visit 5, there was considerable decrease in the tested parameters, except in tender joint count. None of the patients reported any adverse effects, indicating that infliximab biosimilar was well-tolerated in tested patients. **Conclusion:** In this preliminary trial conducted in eight RA patients, treatment with IFB improved clinical outcomes and was well-tolerated in RA patients who failed initial treatment with methotrexate

Key words: Infimab™, BOW015, Rheumatoid arthritis, Efficacy

Introduction

In the management of rheumatoid arthritis (RA), Methotrexate (MTX) the conventional synthetic disease-modifying anti-rheumatic drug (DMARD) is first choice for patients with RA, however response to MTX is not universal and not all patients respond [1] [2]. In RA pathogenesis, tumor necrosis factor (TNF) plays a central role in the pro-inflammatory cytokine cascade [3]. The advent of biological agents including TNF inhibitors has revolutionized the treatment of RA [2]. TNF blockade has shown a remarkable efficacy in reducing joint inflammation, slowing radiographic progression of joint damage, and improving physical function [3].

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In India, about 0.92% of adults are affected by RA and each year 20-40 new cases per lakh population occur. These patients need early diagnosis and aggressive therapy and, in many cases, unfortunately this aggressive therapy is not provided [4]. In addition, RA patients need treatment with costly biologic therapy for long periods of time and also early aggressive therapy is known to have long-term benefits. So in this scenario, availability of relatively low-cost biosimilars may eventually alter the treatment paradigm, allowing RA patients to be treated with less time on DMARDs alone and facilitate in early initiation of biologic therapy. Biosimilars may soon become a mainstay of treatment in RA [5]. International guidelines on the treatment of RA, in particular, have acknowledged the role of biosimilars in terms of their interchangeability with

reference DMARDs, except in the case of lack of efficacy or tolerability [6]. IFB is a novel infliximab biosimilar that is recognized internationally as BOW015. It offers a new opportunity in the management of RA. In September 2014, it became the first infliximab biosimilar to be approved in India, facilitated by Phase 3 clinical data in RA patients [7]. Since two decades infliximab innovator has been used in different clinical trials to assess its efficacy and safety in RA patients with various disease durations [3].

Results from phase I and phase III clinical trials have shown the 'bioequivalence' and 'clinical comparability' of BOW015 to infliximab innovator, as measured by the American College of Rheumatology 20 (ACR 20) response in severe RA patients [8]. Recently the bioequivalence of BOW015 to reference infliximab innovator in healthy volunteers was established, based on single-dose pharmacokinetics, safety, and immunogenicity [9]. Similarly, researchers demonstrated that BOW015 was well-tolerated with similar immunogenicity to infliximab innovator in both the comparative double-blind phase and the open-label switching phase [10]. A team of researchers from Mumbai, demonstrated that IFB was well-tolerated and that majority of the RA patients achieved remission on short-term and long-term basis [11].

There are few preliminary studies on IFB biosimilar, indicating major scarcity in clinical experience in Indian patients, particularly with RA. Therefore, more real life data of IFB efficacy and safety is required, with this intent the current study was undertaken.

Materials and Methods

Study setting: Patients reporting to Orthopedic Department at GB Pant Hospital Port Blair, with active RA were considered for the study.

Inclusion criteria: Age above 18 years, no history of previous biologics,4 months of DMARD (methotrexate) use with no clinical improvement or any improvement in scores, Anti CCP positive.

Exclusion criteria: Previous history of biologics, suspected or confirmed current active tuberculosis (TB), current or past history of chronic infection with Hepatitis B, Hepatitis C, or infection with Human Immunodeficiency Virus-1 or-2 or HBsAG, pregnant women and presence of any form of malignancy.

Sample size: A total of nine patients were recruited, of whom two were male and seven were females. However, one patient was lost to follow-up.

Data collection: Demographics related to age, BMI, occupation, personal history (smoking, tobacco chewing, and alcohol consumption), family history of arthritis, existing co-morbidities and duration of rheumatic disease were also noted.

Scoring: Diagnosis of RA was done according to the revised American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) 2010 classification criteria for RA. Patients with ACR/ EULAR 2010 classification criteria score ≥6 were considered as having RA [12].

Active disease was defined by the presence of erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, C-reactive protein (CRP) ≥ 20 mg/dl, morning stiffness ≥45 min, and swollen and tender joint counts ≥6 each [13]. Patients were screened for tuberculosis (TB) infection.

Procedure: All the patients were given IFB 3mg/kg body weight as intra venous infusion at weeks 0, 2, 6 then every 8 weeks on demand. All patients were continued on methotrexate. After each infusion, patients were observed for 24 hours at the hospital for any adverse effects.

Duration of the study: Eight weeks

Study end points: The primary endpoint was to demonstrate efficacy of this biosimilar, as determined by HAQ (India score), DAS 28 score, WOMAC score, ESR, CPR, Anti-cyclic citrullinated peptide (anti-CCP) levels and VAS score response criteria. The response was assessed in accordance with criteria at the end of each visit.

HAQ (India score) consisted eight categories assessed by the Disability Index are 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. Patients were instructed to score the degree of difficulty accordingly.

The current WOMAC survey form comprised of 24 items divided into three subscales: Pain (5 items), stiffness (2 items), and physical function (17 items).

Patients were asked a range of questions about their ability to carry out daily activities. DAS-28 describes severity of RA using clinical and laboratory data, specifically ESR. Using VAS of 0-100 mm, pain was measured. Blood samples were collected at screening and at every visit to assess ESR, and CRP. Anti-CCP level was tested at baseline visit only.

Ethical consideration and permission: Written informed consent that explained the expected benefit as well as potential adverse effects of infliximab biosimilar was obtained from all patients. Institutional ethical committee approval was obtained.

Statistical analysis: Since, all data is not normally distributed, non-parametric, Wilcoxon sign rank test is used to assess the change between baseline visit to each visits. Data was analyzed using Statistical Package for the Social Science V22.

Results

A total of eight patients were recruited, of whom one was male and seven were females and other demographic details are mentioned Table 1. The total mean age of the patients sampled was 40 years, total mean BMI was 28.9 (23.1–38.7) kg/m^2 and the total mean duration of rheumatic disease history was 4.8 years. None of the patients had history of alcohol intake and smoking. Only one patient had a family history of arthritis. All patients were on MTX for minimum of 1 year. None of the patients had history of TB or active TB. On an average 3 injections of IFB were administered.

Table-1: Demographic details.

Total patients		8
Age in years (Mean)		40 years (range 29-56)
Male vs. Female (N)		1 vs. 7
BMI in Kg/m^2 (Mean)		28.9
Mean disease duration in years (Mean)		4.8
Medical history (N)	Diabetes mellitus	2
	Hypertension	1
	Hypo/hyperthyroidism	2
	No co-morbidity	4
Past history of Disease-modifying antirheumatic drugs (DMARD)	1 DMARD	Methotrexate taken on an average for 1 year

Table-2: Change in parameter values between baseline visit to each visits (Median, p value)

	Baseline	Baseline-Visit 2	Baseline-Visit 3	Baseline-Visit 4	Baseline-Visit 5
HAQ score	1.81	1.313 (p=0.105)	1.250 (p=0.046)	1.000 (p=0.285)	1.13 (p=0.655)
DAS 28 score	5.49	5.15 (p=0.12)	4.63 (p=0.18)	4.78 (p=0.285)	4.55 (p=0.180)
WOMAC score	49	37 (p=0.017)	28 (p=0.018)	29 (p=0.109)	30 (p=0.317)
VAS pain score	62	55 (p=0.176)	44 (p=0. 141)	46 (p =0.285)	45 (p =0.655)
ESR values	43	34 (p=0.090)	25 (p=0.063)	35 (p=0.285)	20 (p=0.180)
Tender joints	8	7 (p=0.231)	3 (p=0.027)	5 (p=0.180)	7 (p=0.180)
Swollen joints	6	2 (p=0.043)	2 (p=0.027)	2 (p=0.109)	4 (p=0.180)
General health	62	50 (p=0.028)	40 (p=0.043)	38 (p=0.180)	40 (p value not estimable)

Wilcoxon sign rank test

HAQ: Health assessment questionnaire, DAS 28: disease activity score 28, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index score, ESR: Erythrocyte sedimentation rate, VAS: Visual Analogue Scale

Table 2 gives the disease activity parameters at the baseline and at the end of follow-up after starting IFB. Patients' HAQ score improved significantly from 1.81 at baseline to 1.250 at visit 3 (p=0.046) and further reduced to 1.13 at visit 5; DAS 28 score reduced from 5.49 at baseline to 4.55 at visit 5. WOMAC score significantly improved from 49 at baseline to 37 at visit 2 (p=0.017) and further reduced to 28 at visit 3 (p=0.018).

There was decrease in VAS score from 62 at baseline to 45 at visit 5, lowest VAS score was seen at visit 3 (44). ESR values lowered from 43 at baseline to 20 at visit 5, tender joint counts also decreased from 8 at baseline to 3 at visit 3 which was significant (p=0.027). Swollen joint count reduced significantly from 6 at baseline to 2 at visit 2 and visit 3(p=0.027). There was improvement in general health, with scores decreasing significantly from 62 at baseline to 50 at second visit (p=0.028) and 40 at visit 3 (p=0.043).

In all eight patients, biosimilar was well-tolerated. No adverse effects or any infection (TB) was noted during the follow-up period.

Discussion

Infimab™ became the first infliximab biosimilar to be approved in India based on the Phase 3 clinical data in RA patients [7].

In India, only a few studies have been carried out to evaluate the efficacy and safety of this newly launched biosimilar in rheumatoid conditions and majority of studies have be carried out in Ankylosing Spondylitis.

According to Sharma et al., in their results from East India cohort, IFB showed significant improvement in Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with Ankylosing Spondylitis (AS) at the end of 4-6 months of follow-up. The clinical benefits were apparent as early as first dose of infusion [14].

Similarly, study carried out at two centers in South India by Rao et al., demonstrated that at the end of one year IFB was safe, well-tolerated and majority of the AS patients had sustained clinical response with just five doses of infusion. An absolute change of 2.55 (95% CI 0.45-4.65) in ASDAS and 1.69 (95% CI 0.11-3.27) in BASDAI were noted.

There was an absolute change of 41.05 mm/hr (95% CI 28.77 - 53.33) and 30.53 mg/L (95% CI 14.76-46.30) in ESR and CRP values, respectively [15]. Agarwal et al., showed that AS patient treated with IFB had significant improvement in $ASDAS_{CRP}$ and BASDAI on a six month follow up period and the clinical benefits were apparent as early as first infusion [16].

These are few preliminary studies on this infliximab biosimilar, indicating major scarcity in clinical experience with IFB in Indian patients, particularly in RA.

In the current study, eight RA patients treated with IFB showed significant improvement in HAQ score, WOMAC score, tender joints count, swollen joints count and general health. It is important to note that, improvement in most of these parameters were apparent as early as second dose of infusion. Though there was decrease in DAS 28 score, VAS score and ESR values from the baseline and follow-up, it was not found to be significant.

A team of researchers from Mumbai in their study demonstrated better clinical improvements. They demonstrated that IFB was well-tolerated and that majority of the RA patients achieved remission on short-term and long-term basis. Further, about 87% patients and 89% patients attained remission at 6 months and 12 months, respectively.

The mean difference at 6 months and 12 months in Simple Disease Activity Index (SDAI) from baseline was 13.15 and 22.61, in body weight was –1.75 and –3.30, in tender joint count was 5.63 and 9.75, swollen joint count was 2.55 and 2.75, in Hemoglobin was –0.67 and –1.15, CRP was 15.03 and 29.07 and in ESR was 14.26 and 12.76, respectively [11].

Kay et al., 2014 and 2015 also showed significant clinical improvement with BOW015 in RA patients [17] [18]. According to the Kay et al., 2014 results, ACR20 responses at week 16 for BOW015 and infliximab innovator, respectively, were 89.9% and 86.4% in per protocol RA population and 85.0% and 85.5% in the intention-to-treat RA population. Their study results provided convincing evidence of therapeutic equivalence. The high ACR20 response rates were consistent with those observed in other RA clinical trials in which patients had not failed MTX and were all treated with an active drug [17].

The same team of researchers conducted a phase 3 trial to evaluate the therapeutic equivalence of BOW015 and reference infliximab innovator in subjects with active RA in a 54─week trial.

According to the results, at week 16, there was clinically significant improvement from baseline in both scores for both groups: mean (±SD) DAS28─CRP: –2.6 (1.3) for BOW015. Disease activity and physical function was similar for BOW015 and infliximab innovator throughout the double-blind and open-label phases of the study, demonstrating durability of the clinical response to BOW015 through 54 weeks.

Along with analytical, pharmacokinetic, and safety data, these results establish bio similarity between BOW015 and infliximab innovator [18].

In a similar trial, Taylor et al. examined the effectiveness of infliximab innovator and compared the efficacy of this treatment to BOW015 in RA patient subgroups with severe or moderate disease activity. The researchers demonstrated that the proportion of ACR20 responders to BOW015 was comparable across sub-groups of RA, as assessed by DAS28 and CRP. Therefore, the increased financial burden of widening access of biologics to patients with moderate disease activity could be offset by use of less expensive biosimilars [19].

In order to shed more light on the use of BOW015 in RA patients, the UNIFORM study is undertaken. This is a prospective, randomized, double-blind, parallel group, multicentre global phase 3 study which is aimed at evaluating and comparing the efficacy, safety and immunogenicity of BOW015 against infliximab innovator in subjects with active RA despite MTX therapy.

However, the results of this study are awaited. It is anticipated that the UNIFORM study results will further position the role of BOW015 in the RA management [12].

Limitation of the study: Study has limitations since it is a preliminary observational study with small patient number from single outpatient orthopedic department.

Conclusion

According to our clinical experience, treatment with Indian Infliximab biosimilar has shown to improve clinical response and was well-tolerated in RA patients who failed initial treatment with methotrexate.

What this study adds to existing knowledge?

There is dearth of clinical evidence on the use of IFB biosimilar, particularly in RA patients in India. To our knowledge, this is the second study carried out among Indian RA patients, apart from a team of researchers from Mumbai. This study provides preliminary efficacy data of IFB biosimilar in RA patients who have failed initial methotrexate treatment, which can be helpful in clinical practice.

Author's contribution

Dr. Nitesh Kaura: Concept designing and conducting the study.
Dr. Amit Ray: Manuscript development and procuring ethical committee permission.
Dr. Amit Kumar: Research and patient follow up

Conflict of interest: None declared.
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